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Mechanisms of the aerobic oxidations catalyzed by *N*-hydroxyderivatives Enthalpic, polar and solvent effects, "molecule-induced homolysis" and synthetic involvements

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Abstract

Aminoxyl ($R_2N{-}O^{\bullet}$), amidoxyl ($RCO{-}N(O^{\bullet}){-}R$) and imidoxyl ($(RCO)_2N{-}O^{\bullet}$) radicals play a key role in the aerobic oxidation catalyzed by *N*-hydroxyderivatives. The rationalization of the mechanisms of a variety of oxidations is based on thermochemical, kinetic and spectroscopic investigations and on solvent effects and it has suggested new selective synthetic developments. In collaboration with CIBA Speciality Chemicals a new catalytic system resulting from the combination of a persistent macrocyclic aminoxyl radical and the couple $Mn(NO_3)_2/Co(NO_3)_2$ has been developed; it is particularly effective for the aerobic oxidation of alcohols to aldehydes and ketones under mild conditions (air at room temperature and atmospheric pressure); above all it presents the great advantage of an easy recovery and recycling providing the possibility of practical applications. The kinetic investigation of the substituent effect in the oxidation of benzyl alcohols has allowed identifying the rate-determining step of the oxidation. The amidoxyl radicals, generated "in situ" from *N*-hydroxyamide, revealed particularly effective catalysts for the aerobic peroxidation of polyunsaturated fatty acids and esters, which is involved in the origin of several important pathologies, such as tumor initiation and atherosclerosis. The kinetic investigation has contributed to explain the mechanism of the oxidation and to develop the most effective methodology for the synthesis of hydroperoxides. The importance of enthalpic, polar, captodative, solvent effects and "molecule-induced homolysis" has been emphasized in the oxidation, halogenation and acetoxylation of a variety of classes of organic compounds (hydrocarbons, alcohols, aldehydes, amines, amides, silanes) by O_2 and *N*-hydroxyimide catalysis. The high selectivity often observed and the very mild experimental conditions, based on the mechanistic interpretation, provide industrial potentiality to the catalytic processes.

Keywords: Aminoxyl radical; Amidoxyl radical; Imidoxyl radical; Polar effect; Enthalpic effect

1. Introduction

The oxidation of organic compounds is one of the most important transformations of the chemistry with fundamental involvements in many areas (general synthesis, industrial processes, materials, energy, biology, etc.). A great variety of oxidants, including transition metal salt complexes (Mn, Cr, Co, Ru, Os, Ce, etc.) are still widely utilized. However, nowadays, the ecological standards require the development of new catalytic processes characterized not only by oxidant-economy, but also by environmental benignity under mild conditions. O_2 is, obviously, a very convenient and potent oxidant, but its direct utilization is restricted by the spin conservation due to the triplet ground state structure, thus, catalysis is necessary for the aerobic oxidations under mild conditions. Both homogeneous and heterogeneous catalysis have been largely utilized.

Two mechanisms are generally involved in catalyzed aerobic oxidations: (i) the oxygenation of the organic compounds by O_2 through chain processes, in which the catalyst takes part in both the initiation and propagation steps; (ii) the direct oxidation of the organic compounds by the catalysts, which are then regenerated by O_2. We have investigated the mechanisms of the aerobic oxidations catalyzed by *N*-hydroxyderivatives, on thermochemical and kinetic basis, providing a quantitative evaluation of the overall catalysis; the mechanistic rationalization has then suggested further synthetic developments [1–3].

2. Oxidation of alcohols

The aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes, carboxylic acids and ketones is an important transformation in organic chemistry.

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The rates of oxidation of aldehydes are always higher than those of the oxidation of the corresponding primary alcohols in the uncatalyzed autoxidation, characterized by a free-radical chain process.

Enthalpic and polar effects widely justify this behavior: the hydrogen abstraction by the peroxyl radicals is rate determining in both cases (Eqs. (1) and (2)):

$$\underset{\sim 88\ \text{kcal/mol}}{\text{RCO–H}} + {}^{\bullet}\text{OOCOR} \xrightarrow{k_1} \underset{\sim 93\ \text{kcal/mol}}{\dot{\text{R}}\text{CO}} + \text{RCOOO–H} \quad (1)$$

$$\underset{\sim 88\text{–}93\ \text{kcal/mol}}{\text{RCHOH–H}} + {}^{\bullet}\text{OOCHOHR} \xrightarrow{k_2} \underset{\sim 88\ \text{kcal/mol}}{\dot{\text{R}}\text{CHOH}} + \text{RCHOHOO–H} \quad (2)$$

From enthalpic point of view reaction (1) is always exothermic, while reaction (2) is either thermoneutral (with benzyl alcohols) or endothermic (with aliphatic alcohols).

The rates of both Eqs. (1) and (2) are also affected by the polar effect (Eqs. (3) and (4)):

$$\text{RCO–H} + {}^{\bullet}\text{OOCOR} \rightarrow \left[\overset{\delta+}{\text{RCO}} \cdots \text{H} \cdots \overset{\delta-}{\text{OOCOR}}\right]^{\neq} \rightarrow \dot{\text{R}}\text{CO} + \text{RCOOO–H} \quad (3)$$

$$\text{RCHOH–H} + {}^{\bullet}\text{OOCHOHR} \rightarrow \left[\overset{\delta+}{\text{RCHOH}} \cdots \text{H} \cdots \overset{\delta-}{\text{OOCHOHR}}\right]^{\neq} \rightarrow \dot{\text{R}}\text{CHOH} + \text{RCHOHOO–H} \quad (4)$$

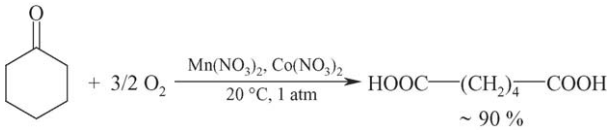
The acyl peroxyl radical of Eq. (3), however, is significantly more electrophilic compared to the peroxyl radical of Eq. (4). Thus, both enthalpic (Eqs. (1) and (2)) and polar effect (Eqs. (3) and (4)) contribute to make $k_1 \gg k_2$.

This behavior has often led to the commonplace that aldehydes are always more reactive than the corresponding primary alcohols in the aerobic oxidations, when oxygen-centered radicals are involved, even if the autoxidation is catalyzed. Actually, that is not the case [4], as it will be discussed later on in the free-radical catalyzed aerobic oxidation of the alcohols; it is not the case, obviously, for the aerobic oxidations in which free-radical hydrogen abstractions are not involved.

As concerns secondary alcohols, enthalpic and polar effects, on the contrary, contribute to make the alcohols much more reactive than the corresponding ketones in uncatalyzed autoxidation. For example the bond dissociation enthalpies (BDE) values of all the C–H bonds in cyclohexanone [5] are higher (C–H in α position 94.1 kcal/mol and C–H in β and γ position 98 kcal/mol) than the BDE value of the C–H bond in $(R)_2$COH–H of cyclohexanol [6] (92.4 kcal/mol).

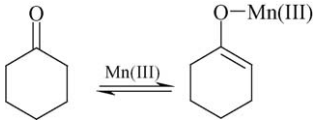
On the other hand the carbonyl group deactivates by polar effect the hydrogen abstraction by peroxyl radicals, while the hydroxyl group activates the $(R)_2$COH–H bond (Eq. (4)) further on contributing to the higher reactivity of cyclohexanol.

Also this behavior has led to another commonplace that secondary alcohols are in all cases more reactive than the corresponding ketones towards the catalyzed aerobic oxidation, in which peroxyl radicals are involved. That is not always the case, as we have recently reported [4]. For example cyclohexanone is selectively oxidized by O_2 to adipic acid under very mild conditions, if the couple of metal salts $Mn(NO_3)_2$/$Co(NO_3)_2$ is utilized as catalyst (Eq. (5)) while cyclohexanol is completely inert under the same conditions:



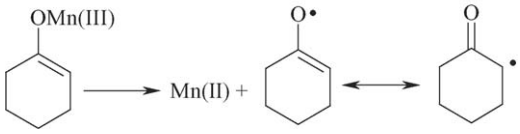
(5)

The mechanism of this catalysis well explains the different reactivity between cyclohexanone and cyclohexanol; the metal salt has two functions: (i) as Lewis acid it catalyzes the enolization of the ketone (Eq. (6)):



(6)

(ii) it determines a redox chain leading to adipic acid (Eqs. (7)–(12)):



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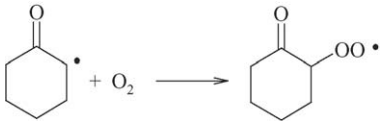

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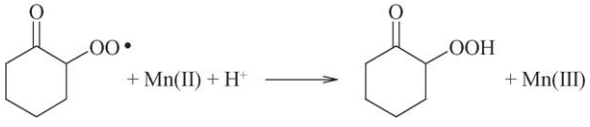

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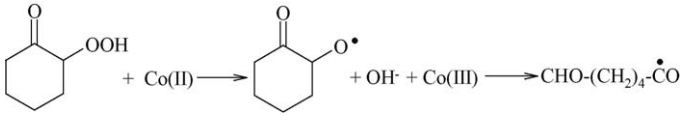


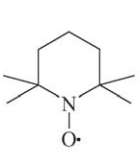
(10)

$$\text{CHO–(CH}_2)_4\text{–}\dot{\text{C}}\text{O} \xrightarrow[\text{Mn(NO}_3)_2,\text{Co(NO}_3)_2]{\text{O}_2} \text{HOOC–(CH}_2)_4\text{–COOH} \quad (11)$$

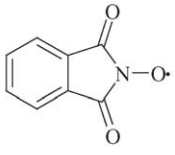
$$\text{Co(III)} + \text{Mn(II)} \rightarrow \text{Co(II)} + \text{Mn(III)} \quad (12)$$

The manganese salt plays the key role in electron-transfer oxidation (Eq. (7)), while the cobalt salt is more effective in the redox decomposition of the hydroperoxide (Eq. (10)).

The aerobic oxidation of alcohols, catalyzed by *N*-hydroxy derivatives, has provided two clear prototypes of the general mechanisms mentioned in the introduction of this paper: two typical catalysts are persistent nitroxyl radicals, such as TEMPO, in which the oxidation of the alcohol is determined by the catalyst, which is then regenerated by O_2, and non-persistent nitroxyl radicals, such as phthalimido-*N*-oxyl (PINO) radical, generated "in situ" from *N*-hydroxyphtalimide (NHPI), which induces selective free-radical chain oxidations directly involving O_2.



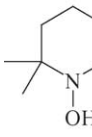
TEMPO



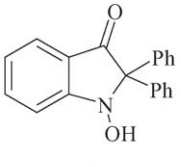
PINO

We have identified on quantitative basis the causes of the different catalytic mechanisms by the two *N*-oxyl radicals, by thermochemical and kinetic investigations, which have allowed to emphasize the importance of the enthalpic and polar effects on the aerobic oxidation of alcohols catalyzed by TEMPO and PINO.

A thermochemical study was undertaken in order to investigate the effect of alkyl, aryl and carbonyl substituents on the BDE values of the O–H bond in a series of *N*-hydroxyderivatives (**1**–**8**).



1



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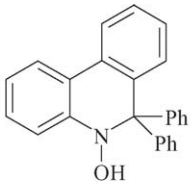

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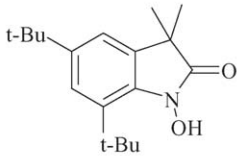

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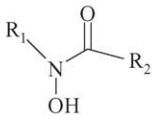


6 R_1 = Me, R_2 = Ph

7 R_1 = CMe_3, R_2 = 3,5$(NO_2)_2C_6H_3$

The EPR radical equilibration technique [1] has been used in order to determine the BDE values of the O–H bonds by measuring the equilibrium constant for the hydrogen transfer between the *N*-hydroxyderivative, a suitable reference compound, AH, whose BDE value is known, and the corresponding radicals (Eq. (13)):

$$R_2N{-}OH + A^{\bullet} \overset{K_e}{\rightleftharpoons} R_2N{-}O^{\bullet} + AH \quad (13)$$

The BDE values were calculated by Eq. (14) by using the known BDE value of A–H and reported in Table 1:

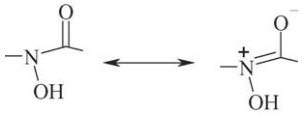
$$BDE(R_2N{-}OH) = BDE(A{-}H) - RT \ln K_e \quad (14)$$

Table 1
BDE values of O–H bonds for *N*-hydroxyderivatives **1**–**8**

N-hydroxyderivative	BDE (kcal/mol^{-1})
1[a]	69.6
2	70.6
3	71.4
4	69.7
5	78.5
6	79.2
7	80.2
8	88.1

[a] Ref. [7].

The carbonyl groups adjacent to the nitrogen atom considerably increases the BDE values of the O–H bonds in the *N*-hydroxy derivatives. Three factors, which induce the stabilization of the acyl hydroxyl amines (Eq. (15) and structure **9**) and the destabilization of the nitroxyl radical (Eq. (16)), appear to be important in increasing the strength of the O–H bonds [1,4]:



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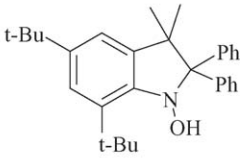

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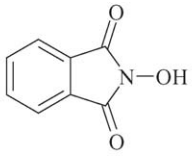

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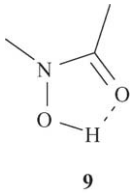

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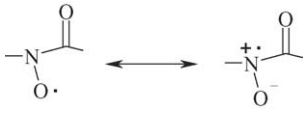
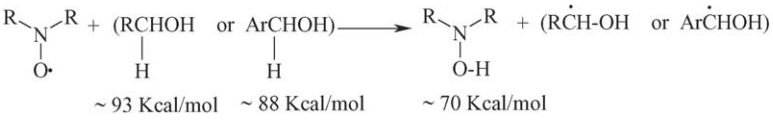


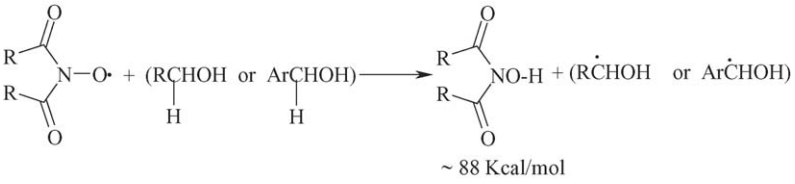
(16)

The same effect of the acyl group was observed in the BDE values of O–H bonds of alcohols (∼104 kcal/mol) compared to carboxylic acids (∼110 kcal/mol) and of hydroperoxides (∼88 kcal/mol) compared to peracids (∼93 kcal/mol).

The BDE values reported in Table 1 clearly indicate that the hydrogen abstraction from C–H bonds of alcohols by aminoxyl radicals is always too endothermic (Eq. (17)) to occur under mild conditions, while it is almost thermoneutral (benzyl alcohols) or moderately endothermic (aliphatic alcohols) by imidoxyl radicals (Eq. (18)), justifying the hydrogen abstraction on thermochemical basis:

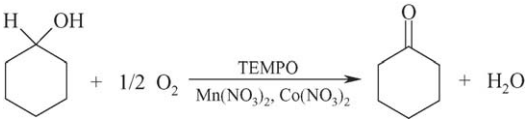


(17)



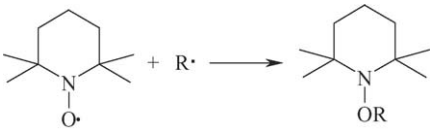
(18)

The non-radical nature of the aerobic oxidation of alcohols catalyzed by persistent aminoxyl radicals, such as TEMPO, was clearly shown by the catalytic system reported by us [2,8], in which TEMPO is associated with the same couple of metal salts, $Mn(NO_3)_2$/$Co(NO_3)_2$ (Eq. (19)), utilized for the free-radical oxidation of cyclohexanone to adipic acid under mild conditions (Eqs. (5)–(12)):



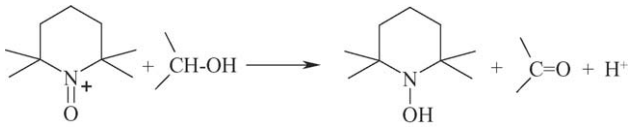
(19)

Under the same conditions of Eq. (19), but in the absence of TEMPO, cyclohexanone is readily oxidized to adipic acid by free-radical chain (Eq. (5)), while cyclohexanol is quite inert. Thus, TEMPO has two basic functions during the catalysis of Eq. (19): it catalyses the oxidation of cyclohexanol, but it also inhibits further aerobic oxidation of cyclohexanone, being a persistent radical which rapidly reacts with a variety of different radicals (Eq. (20)) breaking free-radical chains:



(20)

The mechanism of oxidation of alcohols catalyzed by TEMPO by a variety of oxidants (sodium hypochlorite [9], trichloroisocyanuric acid [10], sodium chlorite [11], sodium bromite [12], periodic acid [13], persulfate [14], and perbenzoic acids [15]) has been ascribed to the formation of the oxammonium ion [16] (Eq. (21)); the function of the oxidant is related to the regeneration of the oxammonium ion from the *N*-hydroxy-derivative:

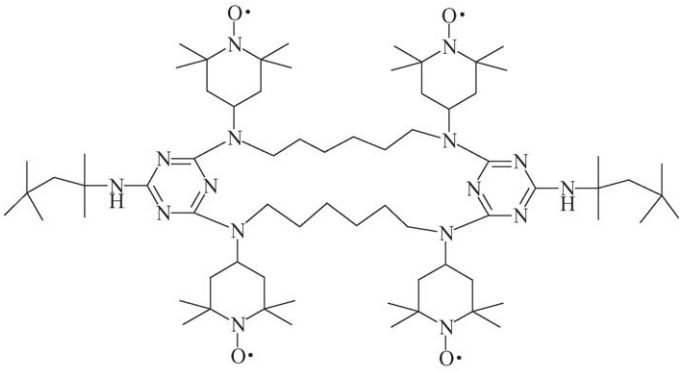


(21)

The aerobic oxidation of alcohols, catalyzed by TEMPO in combination with transition metal salt complexes, has also been utilized [17–20].

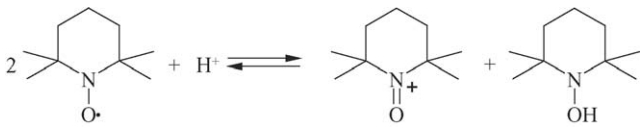
Several groups [21–24] have addressed the problem of recycling the rather expensive nitroxyl radical by anchoring it to solid supports; the heterogeneous catalysis, however, appears to be less effective for the aerobic oxidation of alcohols.

We have developed in collaboration with CIBA Specialty Chemicals a macrocyclic nitroxyl radical, **10**, in combination with $Mn(NO_3)_2$ and $Co(NO_3)_2$, which acts in homogeneous solution as ammonium salt and it is even more active than TEMPO for the aerobic oxidation of alcohols to aldehydes and ketones, but above all **10** presents the great advantage of its easy recovery and recycling and therefore the possibility of industrial applications.



10

The catalysis is effective only in acidic medium suggesting that the oxammonium ion is generated by the disproportionation of nitroxyl radical (Eq. (22)):



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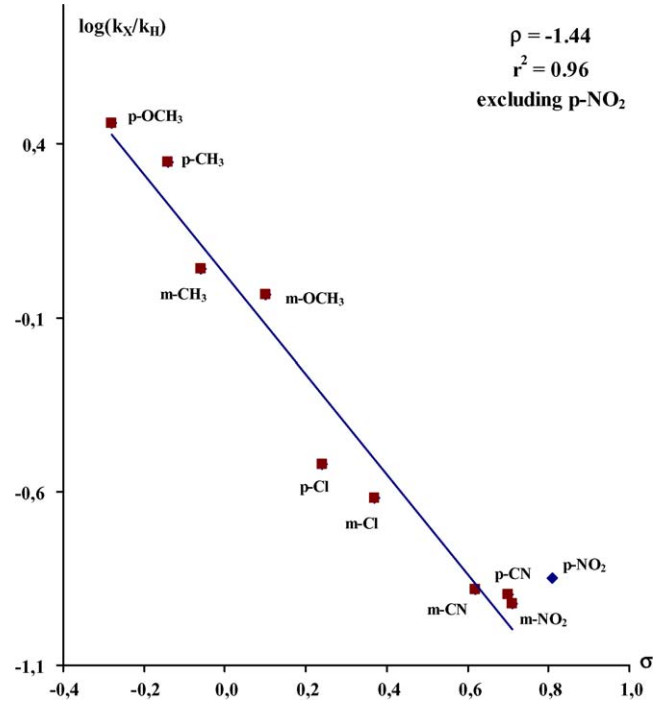
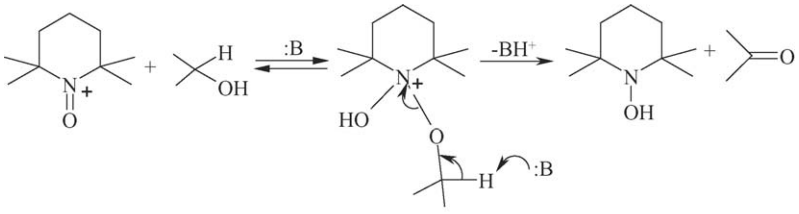


Fig. 1. Substituent effect in the aerobic oxidation of substituted benzyl alcohols with **10** catalysis.

The function of O_2 in combination with $Mn(NO_3)_2$ and $Co(NO_3)_2$ is to regenerate the nitroxyl radical from the *N*-hydroxy-derivative formed in Eqs. (21) and (22).

The mechanism of Eq. (21) was not completely clear and we have investigated the effects that the substituents on the aromatic ring have on the rates of the aerobic oxidation of benzyl alcohols catalyzed by nitroxyl radical **10** protonated by *p*-toluenesulfonic acid. Previous results for the oxidation of alcohols by the oxammonium salts have shown that the hydrogen isotopic effect is higher under acidic conditions ($k_H/k_D = 3.1$) than under basic conditions ($k_H/k_D = 1.8$). These results have suggested that under acidic conditions the rate-determining step should be the α-proton abstraction from the adduct between the alcohol and the oxammonium salt [16], which justify the higher kinetic isotopic effect (Eq. (23)):

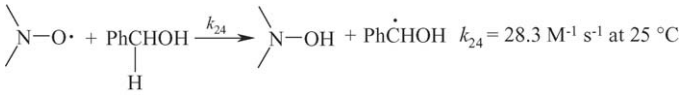


11 (23)

Our results, concerning the effect of the substituents on the oxidation rates of the substituted benzyl alcohols in acidic medium, show that it is not the case. If the α-proton abstraction was the rate-determining step, the electron-withdrawing substituents should favor the oxidation. The Hammett correlation (Fig. 1) of the oxidation rates clearly indicates an opposite behavior: the electron-donating substituents activate and the electron-withdrawing substituents deactivate in agreement with the nucleophilic character of the benzyl alcohols suggesting that the formation of the adduct **11** is mainly rate-determining.

Our interpretation is that the formation of the adduct **11**, which is favored by electron-donating substituents in the benzyl alcohols, occurs almost simultaneously with α-proton abstraction, favored on the contrary by electron-withdrawing substituents; both steps contribute with opposite polar effects to determine the overall rate, but the nucleophilic character of the substituted benzyl alcohol, which affects the addition rate to the oxammonium salt, is always prevailing. This interpretation explains the fact that the polar effect is not high (relatively small value of ρ) and that the Hammett correlation (Fig. 1) is somewhat less satisfactory for the strongly electron-withdrawing substituents, as *p*-NO_2, which particularly increase the rate of the α-proton abstraction and more contribute to partially balance the less marked nucleophilic character of *p*-nitrobenzyl alcohol.

As concerns the aerobic oxidation of alcohols catalyzed by *N*-hydroxyimides the BDE value of the O–H bond (Table 1) justify the hydrogen abstraction from alcohols by imidoxyl radicals (Eq. (18)). On the basis of the pure enthalpic effect, however, no advantage could be recognized for the aerobic oxidation of alcohols catalyzed by NHPI, in which the hydrogen abstraction takes place by the PINO radical, compared to the uncatalyzed autoxidation, in which the hydrogen abstraction is determined by the peroxyl radical because the BDE values of the O–H bonds in NHPI and ROO–H are substantially identical (∼88 kcal/mol). Thus, we have also investigated [1] the rate constant for the hydrogen abstraction from benzyl alcohol by the PINO radical (Eq. (24)), which revealed to be much higher (two orders of magnitude) compared with the hydrogen abstraction by peroxyl radicals (Eq. (25)), in spite of the identical enthalpy variation:



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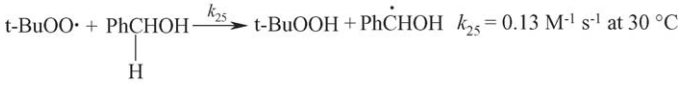
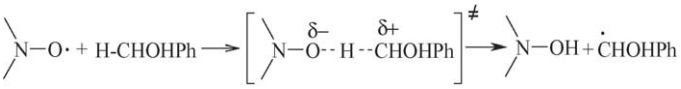


(25)

We have ascribed [2] this large difference of reactivity mainly to the polar effect in relation to a more pronounced electrophilic character of the PINO radical (Eq. (26)) relative to the peroxyl radical (Eq. (4)):



(26)

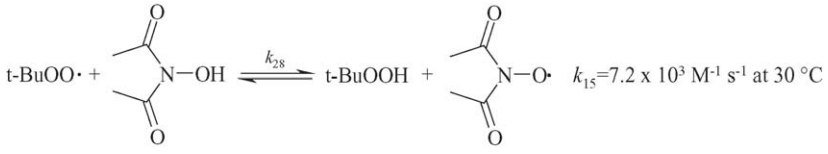
Nitroxyl radicals are generally electrophilic, but this polar character is considerably enhanced by the presence of two carbonyl groups (Eq. (27)):

(27)

Table 2
Absolute rate constants for the hydrogen abstraction from X–C_6H_4–CHOH–H by PINO radical at 25 °C

X	k (M^{-1} s^{-1})
H	28.3
p-Me	65.9
m-Me	48.1
p-OMe	150.0
m-OMe	43.3
p-Cl	35.1
m-Cl	25.7
p-CN	30.6
m-CN	15.2
p-NO_2	27.5
m-NO_2	13.5

by peroxyl radicals (Eq. (28)); it also further on contributes to make quite effective the free-radical chain process of the NHPI catalyzed aerobic oxidations:



(28)

The effect is similar to those observed with acylperoxyl, RC(=O)OO•, and acyloxyl, RC(=O)O• radicals compared to peroxyl, ROO•, and alkoxyl, RO•, radicals; the former are more electrophilic than the latter [25]. The phenomenon is more marked with PINO than with acylperoxyl and acyloxyl radicals because the nitrogen atom can stabilize a positive charge, as in Eq. (27), better than carbon atoms.

The oxidation of alcohols catalyzed by NHPI was first reported [26] in 1977 and afterwards [27] in electrochemical oxidations.

The aerobic oxidation of primary alcohols to carboxylic acids, catalyzed by NHPI, has been reported by the Ishii et al. [28], who did not realize, however, the different behavior of benzylic and aliphatic alcohols. We have shown [29] that the oxidation of primary benzyl alcohols, catalyzed by NHPI leads to aromatic aldehydes in high selectivity and only after the complete conversion of benzyl alcohols does the further oxidation of aromatic aldehydes occurs. In contrast, the oxidation of primary aliphatic alcohols leads to carboxylic acids without significant formation of aldehydes, even at low conversion.

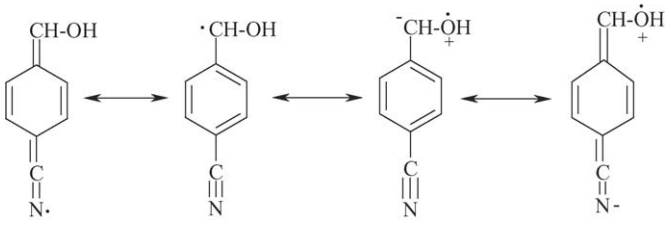
This selectivity clearly indicates that with NHPI catalysis primary benzyl alcohols are much more reactive than the corresponding aromatic aldehydes, while for non-benzyl alcohols the corresponding aldehydes are, in contrast, much more reactive than the starting alcohols. Polar and enthalpic effects well explain this behavior, as it will be discussed later on.

The rate constants of Eqs. (24) and (25) clearly show the importance of the NHPI catalyzed aerobic oxidation compared to the uncatalyzed autoxidation. We have also evaluated [1] the absolute rate constant of the hydrogen abstraction from NHPI

To evaluate the polar effect (Eq. (26)) also in this case we have investigated the influence of substituents on the aromatic ring towards the NHPI catalyzed aerobic oxidation of benzyl alcohols by determining the absolute rate constants (Table 2) for hydrogen abstraction by the PINO radical.

Fig. 2 displays a Hammett correlation between the results of Table 2 and σ^+.

A good correlation was observed with the exception of *p*-nitro and *p*-cyano substituents, which have a negligible effect on the reactivity, while *m*-nitro and *m*-cyano benzyl alcohols are significantly deactivated. We explain this behavior by a captodative effect, which qualitatively [30] suggests that pairs of substituents having opposite polarities act in synergy on the stabilization of a radical according to the resonance structures of Eq. (29):



(29)

From a quantitative point of view, relationships have been observed between the α- and β-proton EPR spectroscopic hyperfine splitting constants and the radical stabilization enthalpy (RSE) and with the BDE values of the corresponding C–H bond [31]. Thus, the captodative effect determines a significant

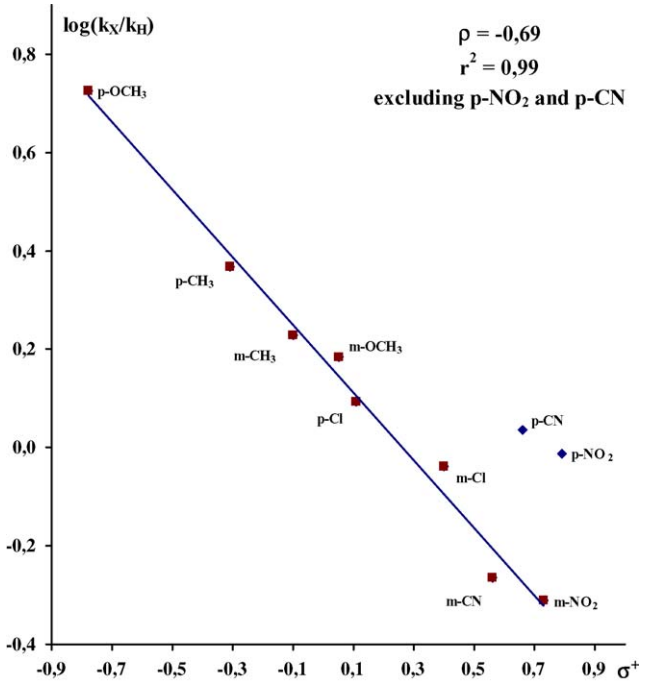


Fig. 2. Substituent effect in the aerobic oxidation of substituted benzyl alcohols with NHPI catalysis.

decreases of the BDE values for benzylic C–H bonds in *p*-cyano and *p*-nitro benzyl alcohol and the favorable enthalpic effect balances the unfavorable polar effect (Eq. (26)). For all the other substituents in Fig. 2 the effect on the BDE values of the benzylic C–H is negligible [32] and a good Hammett correlation is observed.

The selective formation of aromatic aldehydes in the NHPI catalyzed aerobic oxidation is due to the higher rate of hydrogen abstraction from benzyl alcohols by the PINO radical, compared to the hydrogen abstraction from the aldehydes, in spite of the commonplace that aldehydes are more reactive than alcohols in aerobic oxidations. The different reactivity cannot be ascribed to enthalpic effect since the BDE values of the involved C–H bonds in benzyl alcohols [5] and aromatic aldehydes [33] are substantially identical (∼88 kcal/mol), but to a more marked polar effect for the hydrogen abstraction from alcohols (Eq. (26)). The phenomenon appears to be quite general for the hydrogen abstraction from benzyl alcohols and aromatic aldehydes by electrophilic radicals. Thus, the same behavior was observed [33,34] in the aerobic oxidation of benzyl alcohols to aldehydes, catalyzed by a different electrophilic hydrogen abstracting species, the bromine atom Br.

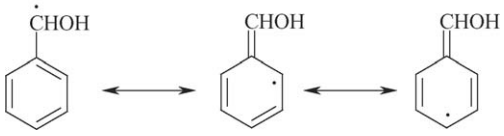
A recent kinetic report [35] that hydrogen abstraction from benzaldehyde by PINO radical is faster than from benzyl alcohol reflects once again the commonplace and it is in clear contrast with our results; we believe that the utilized kinetic methodology [35] was not suitable and that the results are not reliable.

Table 3
BDE values of C–H bonds for alcohols and aldehydes (kcal/mol)

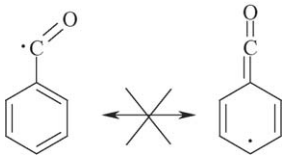
Ph–CHOH–H	**87.5**	Ref. [5]
Me–CHOH–H	**93.0**	Ref. [36]
Ph_2–COH–H	**75.4**	Ref. [5]
Me_2–COH–H	**91.1**	Ref. [37]
Ph–CO–H	**88.7**	Ref. [37]
Me–CH_2CO–H	**88.7**	Ref. [5]

The situation is different with primary aliphatic alcohols; in these cases the enthalpic effect is dominant (the BDE values for RCHOH–H bonds are 5–6 kcal/mol larger than those of RCO–H bonds and that makes the aldehydes much more reactive than the corresponding alcohols, which are selectively oxidized to carboxylic acids, even at low conversions).

The overall behavior is due to the different electronic configuration of benzyl (π-type) and benzoyl radical (σ-type). The benzyl radicals are stabilized by the resonance with the aromatic ring (Eq. (30)); that is not possible with the benzoyl radical (Eq. (31)). Thus, the BDE values of ArCHOH–H bonds are lower than those of RCHOH–H bonds, while the BDE values of ArCO–H are identical to those of RCO–H (Table 3):



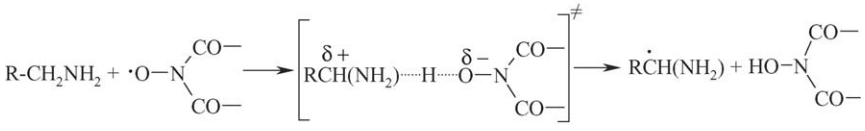
(30)



(31)

3. Oxidations of amines and amides

The amino group is a more effective electron-releasing substituent than the hydroxyl group and it would be expected a stronger polar effect (Eq. (32)) for the hydrogen abstraction by imidoxyl radicals compared to the corresponding alcohols:



(32)

Moreover, Eq. (32) is also more favored by the enthalpic effect, as shown by the BDE values of C–H bonds of Table 4.

Thus, both polar and enthalpic effects suggested a higher reactivity for alkyl amines in the aerobic oxidation, catalyzed by *N*-hydroxyimides, than for alcohols.

Table 4
BDE values of C–H bonds for amines and alcohols (kcal/mol)

Ph–CH(H)–NMe_2	**84.9**	Ref. [6]
Me–CH(H)–NH_2	**90.1**	Ref. [38]
ME_2C(H)–NMe_2	**88.9**	Ref. [38]
Ph–CH(H)–OH	**87.5**	Ref. [5]
Me–CH(H)–OH	**93.0**	Ref. [36]
Me_2C(H)–OH	**91.1**	Ref. [37]

However, primary and secondary amines deactivate *N*-hydroxyimides by Eq. (33) and inhibit the aerobic oxidation:

(33)

t-Amines cannot give an analogous deactivation reaction and are, in fact, easily oxidized under mild conditions [8].

In particular, *t*-benzyl amines give with good selectivity the corresponding aldehydes (Eq. (34)) or ketones (Eq. (35)) by the aerobic oxidation catalyzed by *N*-hydroxy-succinimide (NHSI) or NHPI:

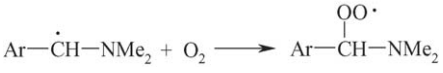
$$ArCH_2NMe_2 + \tfrac{1}{2}O_2 \xrightarrow[70–90\%]{NHSI} ArCHO + Me_2NH \quad (34)$$

$$ArCHR–NMe_2 + \tfrac{1}{2}O_2 \xrightarrow[90–100\%]{NHPI} ArCOR + Me_2NH \quad (35)$$

The higher polar and enthalpic effects and the consequent higher reactivity of amines compared to the corresponding alcohols have been verified by competitive experiments of aerobic oxidation between benzyl amines and the corresponding benzyl alcohols; only the amines are oxidized and only after their complete conversions the oxidation of the alcohols occurs.

For the synthesis of aromatic aldehydes the use of NHSI is more suitable than that of NHPI since it gives a higher selectivity [8]. The reaction mechanism well explains this behavior: the benzyl radical arising from hydrogen abstraction reacts fast with O_2 in a chain process leading to the hydroperoxide (Eqs. (36)–(38)):

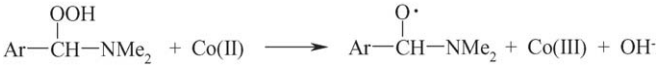
(36)



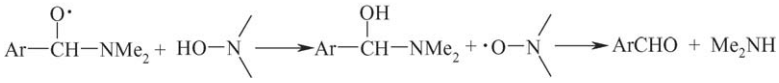
(37)

(38)

The redox decomposition of the hydroperoxide leads to the corresponding alcohol, which is transformed to the aromatic aldehyde (Eqs. (39) and (40)):



(39)

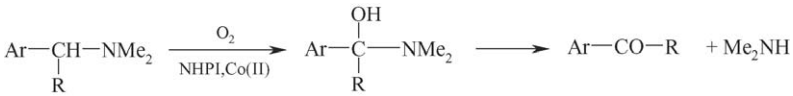


(40)

The selectivity by using NHSI as catalyst is higher compared to NHPI because the hydrogen abstraction by the PINO radical is faster than by the succinimido-*N*-oxyl (SINO) radical. That is reflected with primary benzyl group to the amount of by-product of the oxidation, the amide $ArCONMe_2$, which is higher when the oxidation is catalyzed by NHPI; the amide is formed by the further oxidation of the α-hydroxy amine (Eq. (41)) before its transformation to aromatic aldehyde (Eq. (40)):

$$ArCHOH–NMe_2 \xrightarrow{NHPI} \dot{A}rCOH–NMe_2 \xrightarrow[Co(II)]{O_2} ArCONMe_2 \quad (41)$$

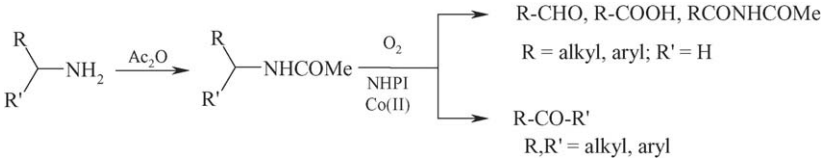
With secondary benzyl groups the ketones are formed with higher selectivity since the α-hydroxy amine cannot be further on oxidized (Eq. (42)):



(42)

As concerns the aerobic oxidation of primary and secondary alkyl amines we have protected the amino group by acetylation in order to avoid the deactivation of the *N*-hydroxy imide catalyst [39] (Eq. (33)).

The polar effect makes the acetamido group less activating compared to the amino group and also the enthalpic effect is less favorable (i.e. the BDE value of $Me_2C(NH_2)$–H bond, 88.9 kcal/mol [38], is lower than that of the corresponding amide, $Me_2C(NHCOMe)$–H, 93.1 kcal/mol [6]). However, both effects are still marked enough for the selective aerobic oxidation of the C–H bonds in α-position to the nitrogen of amides. Thus, the aerobic oxidation of *N*-alkyl amides, catalyzed by NHPI, takes place under mild conditions, particularly in the presence of catalytic amounts of peracids, whose function will be discussed later on, leading to carbonyl products (aldehydes, ketones, carboxylic acids, imides) depending on the structure of the alkyl group and the reaction conditions (Eq. (43)):



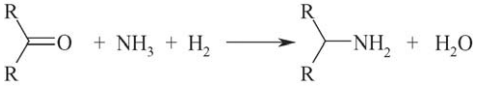
(43)

These aerobic oxidations reproduce the reverse classical transformations of carbonyl derivatives to amines: carboxylic acids can, in fact, be converted to amines through the well-known Hoffmann (Eq. (44)) and Curtius (Eq. (45)) rearrangements [40,41]:

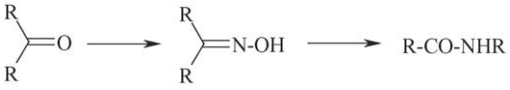
$$RCOOH \rightarrow RCONH_2 \rightarrow RNH_2 \quad (44)$$

$$RCOOH \rightarrow RCON_3 \rightarrow RNH_2 \quad (45)$$

Moreover, aldehydes and ketones can be transformed into aminoderivatives by reductive ammonolysis [42] (Eq. (46)) or Beckmann (Eq. (47)) rearrangements of the oximes [43]:

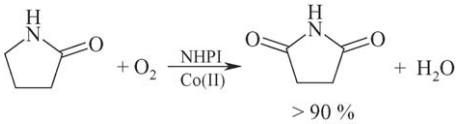


(46)

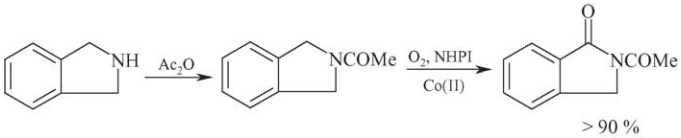


(47)

The catalyzed aerobic oxidation of lactames (Eq. (48)) or cyclic amines (Eq. (49)) is particularly selective [39]:



(48)

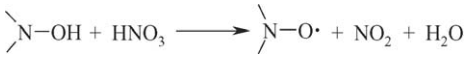


(49)

4. Polar and enthalpic effects in aerobic halogenation of alkanes, catalyzed by NHPI, HNO_3 and Cu(II)

The importance of the polar and enthalpic effects, in reactions in which the hydrogen abstraction from C–H bonds by the PINO radical is rate determining, has been emphasized by the development of a new methodology for the free-radical halogenation of alkanes, catalyzed by NHPI [44].

The EPR spectrum of the PINO radical was readily observed by adding at r.t. 10% aqueous HNO_3 to a solution of NHPI in acetonitrile. According to our interpretation the induced homolysis of NHPI occurs according to Eq. (50):



(50)

NO_2 can further on abstracts a hydrogen atom from NHPI (Eq. (51)) always leading to the PINO radical:

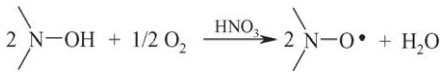
(51)

The process is made catalytic by the presence of O_2 since the disproportionation of HNO_2 leads to HNO_3 and NO (Eq. (52)) and this last is oxidized to NO_2 (Eq. (53)):

$$3HNO_2 \rightarrow HNO_3 + 2NO + H_2O \quad (52)$$

$$2NO + O_2 \rightarrow 2NO_2 \quad (53)$$

Thus, the overall stoichiometry of the oxidation is given by Eq. (54):



(54)

We have considered the possibility of halogenation of alkanes by operating in the presence of HX (X = Cl, Br, I) and catalytic amount of CuX_2, taking advantage of the hydrogen abstraction from the alkanes by the PINO radical (Eq. (55)) and the fast halogen transfer from CuX_2 to the alkyl radical [45] (Eq. (56)):

(55)

$$R^{\bullet} + CuX_2 \xrightarrow{k_{56}} R{-}X + CuX, \quad k_{56} > 10^9\ M^{-1}\ s^{-1} \quad (56)$$

CuX_2 is continuously regenerated from CuX by oxidation with O_2, HNO_3 and NO_2 so that the overall stoichiometry for the halogenation of alkanes is given by Eq. (57):

$$RH + \tfrac{1}{2}O_2 + HX \xrightarrow[HNO_3, Cu(II)]{NHPI} RX + H_2O \quad (57)$$

Table 5
Isomer distribution in halogenation of substituted alkanes, catalyzed by NHPI

	MeOCO—CH_2—	CH_2—	CH_2—	CH_3
Cl_2[a]	5.4	30.1	44.5	18.7
Br_2[a]	35.4	19.6	45.4	-
HCl + O_2 (NHPI)	8.2	27.1	64.7	-
HBr + O_2 (NHPI)	9.4	26.6	64.0	-
HI + O_2 (NHPI)	8.4	26.9	64.7	-
	MeOCO—CH_2—	CH_2—	CH_2—	CH_3
HCl + O_2 (NHPI)	6.1	12.1	28.3	53.5	-
HBr + O_2 (NHPI)	6.3	16.0	27.0	50.7	-
Me_2NCl[b]	-	0.7	6.3	87.3	6.7
Me_2NBr[c]	-	0.4	5.9	87.0	6.8
	O_2N—CH_2—	CH_2—	CH_2—	CH_2—	CH_3
HCl + O_2 (NHPI)	-	-	9.2	32.2	58.6	-

[a]Ref. [46].
[b]Ref. [47].
[c]Ref. [48].

The chemo- and regio-selectivity for the chlorination and bromination according to Eq. (57) are quite different from those of the classical free-radical halogenation by Cl_2 and Br_2, in which $Cl^\bullet$ and $Br^\bullet$ are hydrogen abstracting species, as the results of Table 5 clearly show; the direct iodination of alkanes by I_2 is prevented by the too high endothermicity for the hydrogen abstraction by the iodine atom $I^\bullet$.

In principle, the alkyl radical $R^\bullet$ of Eq. (56) can also rapidly react with O_2, NO, NO_2 (the rates of all these reactions are often diffusion controlled), but the higher concentration of CuX_2 in the reaction medium makes the halogenation quite selective.

The following aspects characterize this new methodology of halogenation:

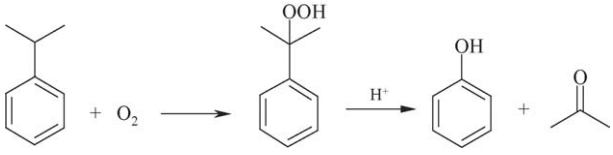
(i) The importance of the polar effect is emphasized by mono-halogenation, even with high conversions, in the reaction catalyzed by NHPI because the introduction of a halogen atom deactivates the mono-halogenated reaction products towards further halogenation; this behavior was observed also with *N*-haloamines (Minisci halogenation) [49], in which the polar effect is particularly marked, due to the positive charge on the hydrogen abstracting species, $R_2\overset{+}{N}H$, but not with the classical halogenation by Cl_2 and Br_2, where polyhalogenation takes place as the conversion increases.

(ii) Classical chlorination and bromination by Cl_2 and Br_2 (iodination by I_2 does not occur) [50] show a quite different selectivity, due to the different contribution of polar and enthalpic effects and to the much higher reactivity of chlorine relative to bromine atoms, whereas chlorination, bromination and iodination show the same selectivity when catalyzed by NHPI, clearly indicating that the hydrogen abstraction from C–H bonds, which represents the rate-determining step, takes place by the same radical (PINO). The same reactivity was also observed for chlorination and bromination by *N*-haloamines, in which the same aminium radical, $R_2\overset{+}{N}H$, is the hydrogen abstracting species [51].

(iii) The enthalpic effect determines the different reactivity between the CH_2 and CH_3 groups, whereas the different reactivity among the CH_2 groups is clearly determined by the polar effect in the halogenation catalyzed NHPI; inductive and field effects make more reactive the CH_2 group farther from the electron-withdrawing substituent, as it is particularly shown by the chlorination of 1-nitrohexane (Table 5).

5. Aerobic oxidation of ispropylaromatics, catalyzed by NHPI, for the synthesis of phenols or isopropenyl derivatives: temperature and solvent effect

The production of phenol from cumene by aerobic oxidation (Eq. (58)) is one of the main industrial chemical processes, which has replaced traditional production:



(58)

Analogous processes have been developed for the production of diphenols from diisopropyl aromatics.

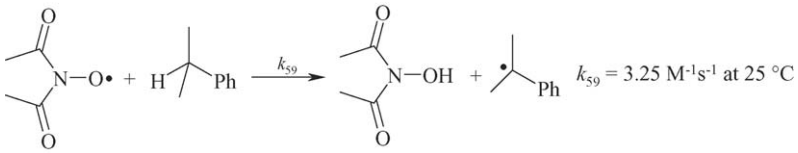
A high selectivity is achieved in the peroxidation of cumene by partial conversions since the free-radical process is characterized by auto-initiation, due to the thermal homolysis of small amounts of the hydroperoxide with the formation of cumyloxyl radical, which initiates free-radical chains of autoxidation and leads to cumyl alcohol and acetophenone as by-products.

Increasing conversions determine a higher concentration of hydroperoxide, which decomposes to a larger extent determining a lower selectivity of peroxidation.

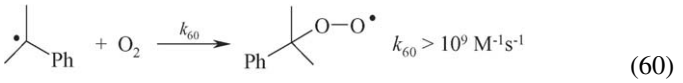
However, the partial conversion is not a serious drawback because the separation of cumyl hydroperoxide from unreacted cumene is not a too complex process.

Additional complexities are encountered in the production of diphenols from diisopropyl aromatics since in these cases partial conversions give mixtures of mono- and di-hydroperoxides, whose separation is much more complex [52].

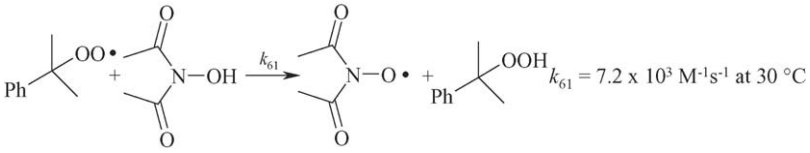
We have determined [1] the absolute rate constants for the hydrogen abstraction from cumene by the PINO radical (Eq. (59)) and the formation of the PINO radical by hydrogen abstraction from NHPI by the peroxyl radical in a chain process (Eqs. (59)–(61)):



(59)

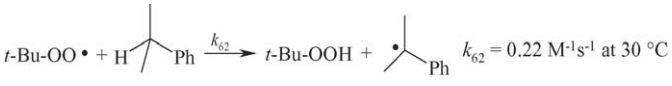


(60)



(61)

These kinetic constants, evaluated for the first time [1], are of relevant interest because they show how the hydrogen abstractions from C–H bonds by the PINO radical are significantly faster than the same hydrogen abstraction by the peroxyl radicals [1,4] (Eq. (62)), in spite of the substantially identical BDE values of the O–H bonds in NHPI and hydroperoxide:



(62)

The consequence is that the aerobic oxidation by the catalytic cycle involving NHPI and PINO radical (Eqs. (59)–(61)) is considerably more effective compared to the classical uncatalyzed free-radical autoxidation and it can be carried out at significantly lower temperatures. We have already discussed the importance of polar effect in the hydrogen abstraction by the PINO radical [44].

In order to obtain useful products based on the mechanistic evaluations of the involved free-radical chains, we have followed different approaches for the selective aerobic oxidation of alkyl benzenes.

The first approach concerns the selective formation of benzyl alcohols by NHPI catalyzed aerobic oxidation (Eq. (63)):

$$2\text{Ar–CHMe}_2 + \text{O}_2 \xrightarrow[\text{Co(II)}]{\text{NHPI}} 2\text{Ar–C(OH)Me}_2 \quad (63)$$

Previous aerobic oxidations of cumene catalyzed by NHPI were carried out by Ishii et al. [28,53] in the presence and in the absence of Co(II) as cocatalyst; in both cases acetophenone was the main reaction product, cumyl alcohol being a minor product.

It is well known that the formation of the acetophenone in the aerobic oxidation of cumene arises from β-scission of the cumyloxyl radical (Eq. (64)), generated by redox or thermal decomposition of the hydroperoxide, while the cumyl alcohol is mainly formed by the very fast ($\sim 10^9\ \text{M}^{-1}\ \text{s}^{-1}$) hydrogen abstraction from NHPI (Eq. (65)) or from cumene (Eq. (66)) when NHPI has been consumed during the reaction:

$$\text{PhCMe}_2\text{–O}^\bullet \xrightarrow{k_{64}} \text{Ph–COMe} + \text{Me}^\bullet \quad (64)$$

(65)

$$\text{PhCMe}_2\text{–O}^\bullet + \text{PhCMe}_2\text{–H} \xrightarrow{k_{66}} \text{PhCMe}_2\text{–OH} + \text{PhCMe}_2 \quad (66)$$

The pioneering research of Walling and Padwa [54] has shown that the solvents have a relevant effect on the magnitude of the ratio between β-scission of the alkoxyl radical and the hydrogen abstraction. Temperature also favors more the unimolecular β-scission (Eq. (64)) than the bimolecular hydrogen abstraction (Eqs. (65) and (66)).

Much more recently Ingold provided conclusive resolution of this long-standing problem concerning the solvent effects on the competitive β-scission and hydrogen abstraction of the cumyloxyl radical by laser flash photolysis. The results have clearly demonstrated that the hydrogen abstraction from C–H bonds is solvent independent; for example the same rate constant ($1.2 \times 10^6\ \text{M}^{-1}\ \text{s}^{-1}$ at 30 °C) was determined for the hydrogen abstraction from cyclohexane (Eq. (67)) in a variety of solvents of different polarity. The rate of β-scission, on the contrary, increases with the increasing solvent polarity (Table 6) and that can be ascribed to increased stabilization of the transition state for β-scission by increased solvatation of the incipient acetophenone product [55]:

$$\text{PhCMe}_2\text{–O}^\bullet + \text{C}_6\text{H}_{12} \xrightarrow{k_{67}} \text{PhCMe}_2\text{–OH} + \text{C}_6\text{H}_{11} \quad (67)$$

A more pronounced solvent effect occurs for the hydrogen abstraction by cumyloxyl radical from hydroperoxide and phenol [56,57] (Eqs. (68) and (69)):

$$\text{PhC(Me)}_2\text{–O}^\bullet \xrightarrow[k_{68}]{t\text{-BuOOH}} \text{PhC(Me)}_2\text{–OH} + t\text{-BuOO}^\bullet \quad (68)$$

$$\text{PhC(Me)}_2\text{–O}^\bullet \xrightarrow[k_{69}]{\text{Ph–OH}} \text{Ph–O}^\bullet + \text{PhC(Me)}_2\text{–OH} \quad (69)$$

The results of Table 7 show that the solvent-induced decrease of the hydrogen abstraction rate is associated with hydrogen

Table 6
Solvent effect on k_{64} and k_{67} rate constants

Solvent	$k_{64} \times 10^5\ \text{s}^{-1}$ at 30 °C	$k_{67} \times 10^6\ \text{M}^{-1}\ \text{s}^{-1}$ at 30 °C
CCl_4	2.6	1.2
C_6H_6	3.7	1.2
C_6H_5Cl	5.5	1.2
Me_3COH	5.8	1.2
MeCN	6.3	1.2
MeCOOH	19.0	1.2

Table 7
Solvent effect on k_{68} and k_{69} rate constants

Solvent	k_{68} ($\text{M}^{-1}\ \text{s}^{-1}$)	$k_{69} \times 10^6\ \text{M}^{-1}\ \text{s}^{-1}$
CCl_4	2.5×10^8	8.6×10^8
Me_3COH	6.7×10^6	3.6×10^6

Table 8
Temperature and solvent effects for the aerobic oxidation of cumene, catalyzed by NHPI and $Co(OAc)_2$[a]

Solvent	T (°C)	Time (h)	Conversion (%)	Cumyl alcohol (%)	Acetophenone (%)
Ph—CN	100	20	76	8	64
AcOH	100	20	40	10	54
t-BuOH	50	24	77	62	38
MeCOMe	50	5	91	68	20
CCl_4	60	24	42	81	19
MeCN	80	8	72	69	31
MeCN	70	24	98	76	23
MeCN	50	24	100	91	9
MeCN	40	9	100	99	–
Ph—Cl	50	24	40	100	–
1,2-$C_6H_4Cl_2$	50	24	64	100	–
1,2-$C_6H_4Cl_2$	100	2	15	100	–

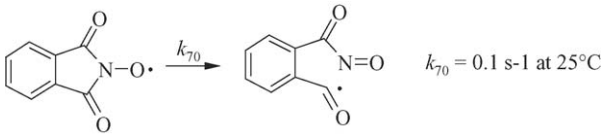
[a] Five millimoles of cumene, 10% NHPI and 0.5% $Co(OAc)_2$, under oxygen at atmospheric pressure.

bonds between the O–H groups of *t*-BuOOH and PhOH and the solvent, which also affect the BDE values of the O–H bonds. The dramatic effect of Table 7 suggested us that an analogous solvent effect should be involved for the hydrogen abstraction from NHPI by the cumyloxyl radical (Eq. (65)).

On the basis of this assumption and of the Ingold's kinetic results we have investigated the effect of the solvents and of the temperature on the aerobic oxidation of cumene, catalyzed by NHPI and Co(II) salt.

The results [3], reported in Table 8, support our expectations as concerns the influence of the temperature and the solvents.

It could appear contradictory to obtain lower conversions at higher temperatures, but that is due, in our opinion, to the lower stability at higher temperature of the PINO radical, whose decay follows a first order kinetics (Eq. (70)); the decomposition of the nitroxyl radical obviously prevents from the catalysis and reduces the conversions:

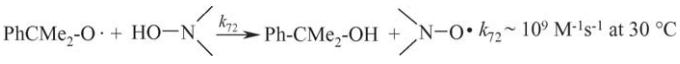


(70)

The results of Table 8 show that solvents such as chlorobenzene would be particularly suitable for the selective synthesis of benzyl alcohols from isopropyl aromatics. However, the low solubility of NHPI in these solvents does not allow high conversions; this is a major drawback for the oxidation of diisopropyl aromatics since a complete conversion of both isopropyl groups is of higher interest for practical applications of the process. A high solvent polarity increases the solubility of NHPI, but at the same time it reduces the selectivity to benzyl alcohol. A compromise has been achieved with solvents, as acetonitrile, which grants a satisfactory solubility for the catalyst while allowing complete conversion for diisopropyl aromatics at a temperature low enough to favor a high selectivity to benzyl alcohol. The low temperature also favors the recovery and recycle of NHPI because it reduces the self-decay of the PINO radical (Eq. (70)).

Thus, the overall mechanism involves the free-radical chain of Eqs. (59)–(61) leading to the hydroperoxide; the redox decomposition of this last leads to benzyl alcohol by the free-radical redox chain of Eqs. (71)–(73):

(71)

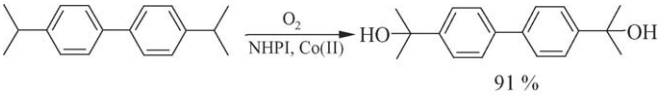


(72)

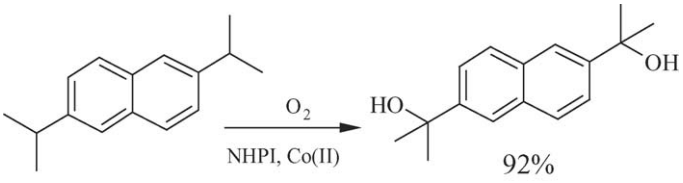
(73)

The combination of the effects of the solvent and of the temperature and the high rate constant of Eq. (72) prevents from the β-scission of the cumyloxyl radical (Eq. (64)) leading to complete conversion and high selectivity in benzyl alcohol.

The best conditions, reported in Table 8, were utilized for the aerobic oxidation of 4,4′-diisopropyl-diphenyl and 2,6-diisopropyl-naphthalene [3]; complete conversions and high selectivity were obtained in both cases (Eqs. (74) and (75)):

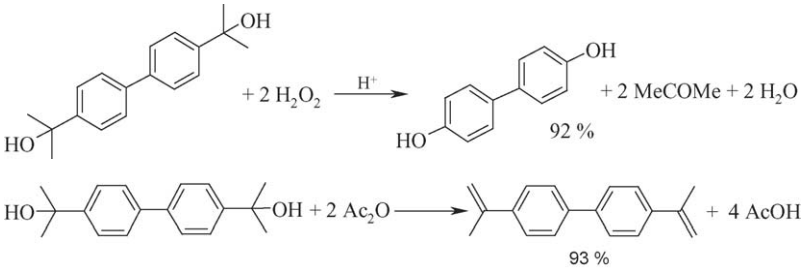


(74)



(75)

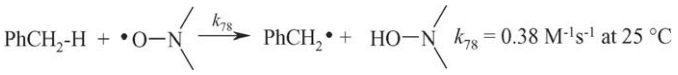
The benzyl alcohols were transformed in diphenols (Eq. (76)) and diisopropenyl derivatives (Eq. (77)) respectively useful monomers for liquid crystals and cross-linked polymers, by reaction with H_2O_2 or Ac_2O [3]:



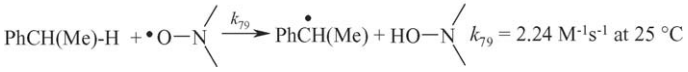
(76)

(77)

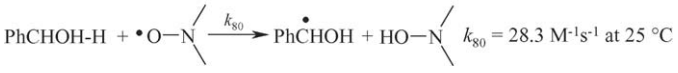
Primary and secondary benzyl alcohols cannot be obtained by these procedures for the simple reason that the alcohols initially formed are more reactive than the starting alkyl aromatics towards the hydrogen abstraction by the PINO radical [1,4] (Eqs. (78)–(80)):



(78)

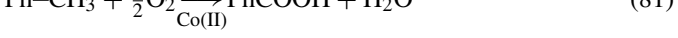


(79)

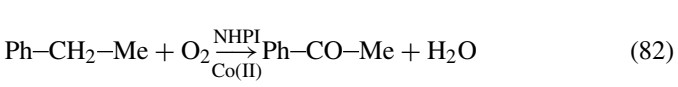


(80)

Thus, the oxidation of toluene and ethylbenzene, catalyzed by NHPI and Co(II) salt, mainly leads to benzoic acid and acetophenone, even with partial conversions (Eqs. (81) and (82)):



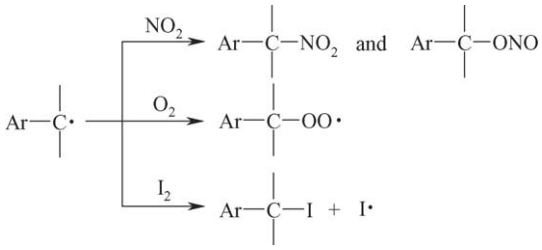
(81)



(82)

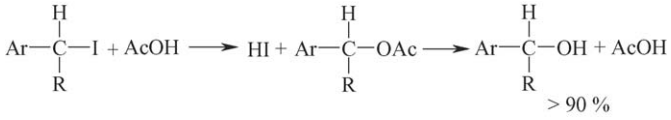
In order to obtain primary and secondary alcohols by aerobic oxidation of alkyl aromatics we have utilized a different strategy, based on the catalysis by NHPI in association with HNO_3 and I_2 in acetic acid solution [58].

The PINO radical is formed according to Eqs. (50) and (51), before discussed; the hydrogen abstraction by the PINO radicals from alkyl aromatics leads to benzyl radicals (Eqs. (78) and (79)), which react very fast (close to diffusion controlled rate) with I_2, O_2, NO_2 (Eq. (83)):



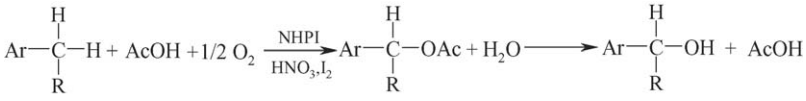
(83)

However, benzyl iodides are selectively formed by keeping the stationary concentration of I_2 much higher than those of NO_2 and O_2. Under the reaction conditions the benzyl iodides undergo solvolysis to benzyl acetates (Eq. (84)), which are obtained with high yields; the subsequent hydrolysis leads to the corresponding benzyl alcohols:



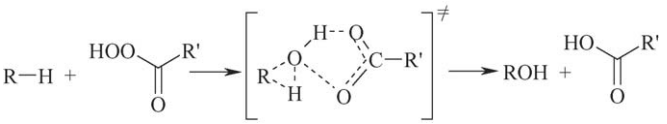
(84)

The process is catalytic in NHPI, HNO_3 and I_2 because HNO_3 and I_2 are respectively regenerated by O_2 oxidation of NO, formed in Eq. (52), and of HI arising in Eq. (84). Thus, the overall stoichiometry is given by Eq. (85):

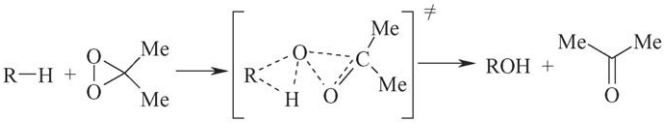


(85)

A different approach for the synthesis of phenols through the catalytic peroxidation of isopropyl aromatics has been developed by us, taking advantage of "molecule-induced homolysis" of NHPI by peracids or dimethyldioxirane. Few years ago we have explained the oxidation of a variety of organic compounds (hydrocarbons, alcohols, ethers, aldehydes, etc.) by peracids [25] and dioxiranes [59], in contrast with the generally accepted mechanism of "concerted oxenoid oxygen insertion" [60,61], which postulates butterfly type transition states (Eqs. (86) and (87)), similar to the one originally suggested by Bartlett [62] for alkene epoxidation by peroxides:

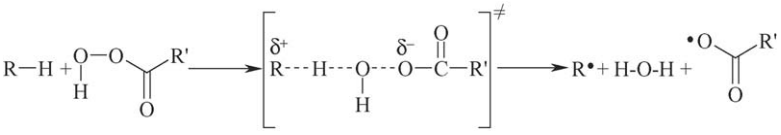


(86)

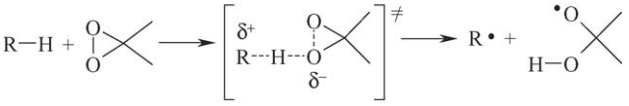


(87)

Our interpretation is based on the "molecule-induced homolysis", in which the transition states are related to the hydrogen abstractions with formation of radical pairs (Eqs. (88) and (89)):



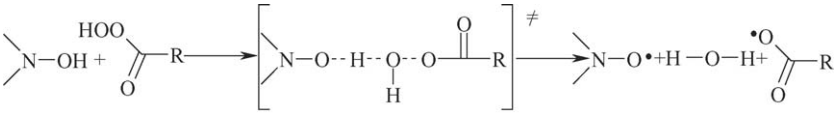
(88)



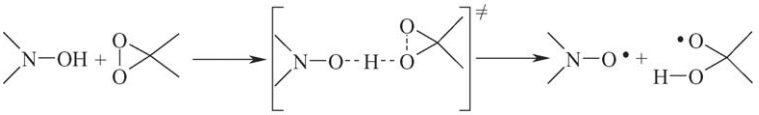
(89)

We have ascribed the driving force for Eqs. (88) and (89) to the high BDE values of the O–H bonds formed in hydrogen abstractions, which are particularly effective with weaker C–H bonds (tertiary alkyl, benzyl, RCO–H, etc.).

The relatively low BDE value (88.1 kcal/mol, Table 1) of the O–H bond for NHPI suggested that peracids and dioxiranes could give induced homolysis of NHPI under mild conditions, generating the PINO radical (Eqs. (90) and (91)), which plays a key role in the aerobic oxidations catalyzed by NHPI, as already discussed:



(90)



(91)

The controversial mechanisms of Eqs. (86)–(89) are intriguing since the fast coupling of the radical pairs, formed according to Eqs. (88) and (89) in the solvent cage (i.e. Eq. (92)), leads to the same reaction products of the insertion mechanism and only few radicals can escape from the cage giving typical free-radical reactions:

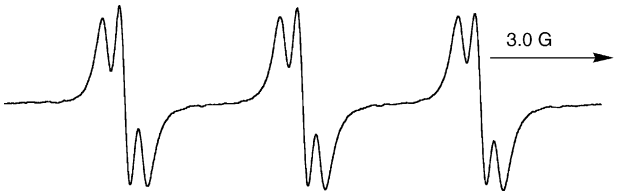
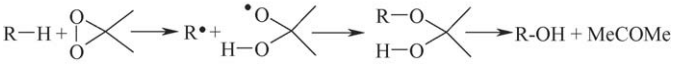
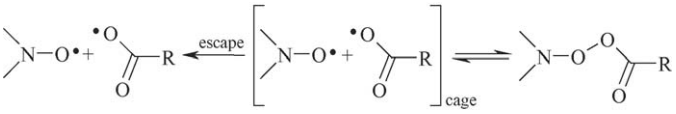


Fig. 3. EPR spectrum of PINO obtained by mixing NHPI with *m*-CPBA in CH_3CN at room temperature.

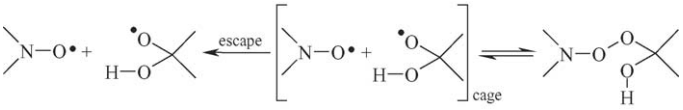


(92)

The hypothetical couplings of the radical pairs generated in Eqs. (90) and (91), if take place (it is difficult to evaluate the BDE values of the O–O bonds in the event of resulting =N–O–O– derivatives), are very likely reversible (Eqs. (93) and (94)) so that the PINO radical and the alkoxyl or the acyloxyl radicals can escape from the solvent cage giving the typical free-radical reactions:



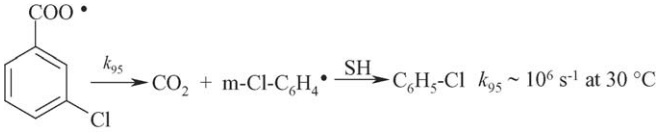
(93)



(94)

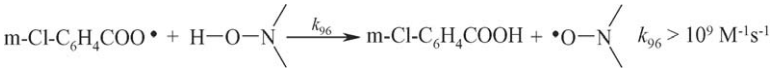
Spectroscopic and chemical investigations have supported this assumption. The EPR spectrum of the PINO radical was readily observed simply by adding at r.t. NHPI to solutions of *m*-chloro-perbenzoic acid in acetonitrile (a(2H) = 0.46 G; a(N) = 4.77 G) or dimethyldioxirane in acetone (a(2H) = 0.44 G; a(N) = 4.70 G), as it is shown in Fig. 3.

Thus, we have considered the possibility to utilize the complex NHPI/peracid and NHPI/dioxirane as catalyst for the aerobic oxidation of hydrocarbons under mild conditions in the absence of metal salts. Actually the selective aerobic oxidation of alkylaromatics and alkanes readily occurs at r.t. and atmospheric pressure. No substantial oxidation occurs in the absence of either NHPI or the peroxides (peracid or dioxirane) in all cases, strongly supporting that the "molecule-induced homolysis" according to Eqs. (90) and (91) are responsible of the catalysis. The hydroperoxides, formed according to the free-radical chains similar to Eqs. (59)–(61), do not induce the aerobic oxidation under the same conditions. A careful analysis (HPLC and GC) of the aerobic oxidations of hydrocarbons, catalyzed by NHPI and *m*-CPBA has provided further evidence of the mechanism of the catalysis; NHPI remains substantially unchanged, whereas *m*-CPBA is transformed mainly to *m*-chloro-benzoic acid and to a smaller amount to chlorobenzene. The only reasonable mechanism for the formation of chlorobenzene is the decarboxylation of the acyloxyl radical [63] and the subsequent hydrogen abstraction from the reaction medium by chlorophenyl radical (Eq. (95)):



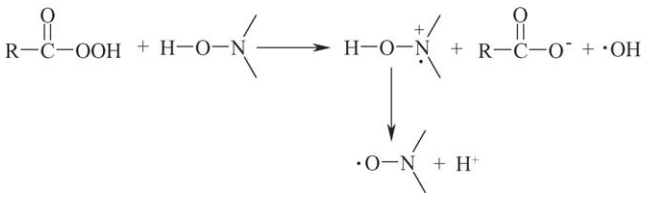
(95)

m-Chloro-benzoic acid is formed by hydrogen abstraction from NHPI by the acyloxyl radical (Eq. (96)), which we expect to be a very fast reaction ($k_{96} > 10^9\ M^{-1}\ s^{-1}$) on the basis of the known rate constants for the hydrogen abstractions from NHPI by peroxyl radical (Eq. (61), $7.2 \times 10^3\ M^{-1}\ s^{-1}$) and alkoxyl radical (Eq. (65), $\sim 10^9\ M^{-1}\ s^{-1}$); Eq. (96) is more exothermic respectively of about 22 and 6 kcal/mol than Eqs. (61) and (65):



(96)

The only possible mechanism alternative to the induced homolysis (Eq. (90)), which could lead to the simultaneous formation of the PINO and the acyloxyl radicals, is an electron-transfer oxidation; however it appears unlikely because a hydroxyl radical should be formed from the peracid (Eq. (97)) rather than an acyloxyl radical:



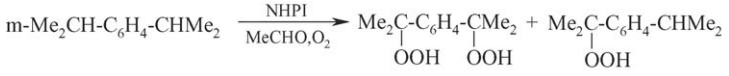
(97)

Thus, spectroscopic and chemical evidences clearly indicate that the formation of the PINO and acyloxyl radicals, according to Eq. (90), is responsible of the overall catalytic process of the hydrocarbon aerobic oxidation under mild conditions.

From synthetic applications the use of peracids is more useful than that of dioxiranes because the peracids can be generated "in situ" from catalytic amounts of cheap aldehydes, as acetaldehyde or banzaldehyde, under the aerobic oxidation conditions:

$$R\text{–}CHO + O_2 \xrightarrow{NHPI} R\text{–}COOOH \quad (98)$$

With tertiary C–H bonds the corresponding hydroperoxides are obtained with high selectivity under mild conditions. Thus, *m*-diisopropylbenzene gives high conversions and high selectivity of hydroperoxides at r.t. and atmospheric pressure of O_2 (Eq. (99)):

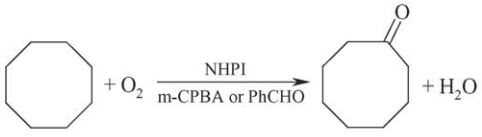


Conversion 100 %, Selectivity: 76% dihydroperoxide
24% monohydroperoxide

(99)

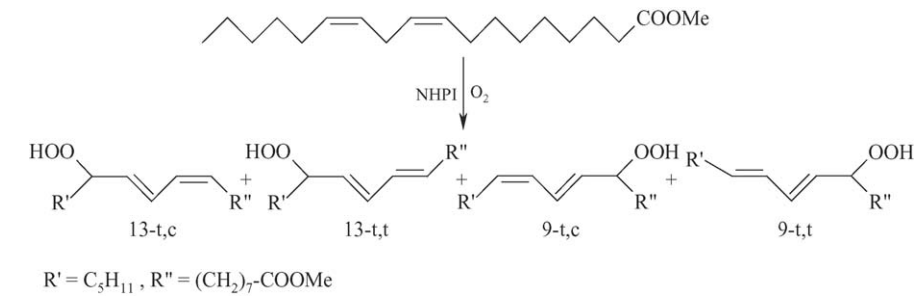
The monohydroperoxide can be further on converted to dihydroperoxide by light increase of temperature (40–50 °C) and by increasing the reaction time. The low temperature allows also to utilize solvents, such as acetic acid, which inhibit the aerobic peroxidation when the reaction is catalyzed by NHPI at higher temperatures [64], due to the formation of phenols, which act as chain-breaking inhibitors. Moreover, the low temperature prevents from the self-decay [1] ($0.1\ s^{-1}$ at 30 °C) of the PINO radical and NHPI remains substantially unchanged at the end of the reaction.

With secondary C–H bonds the aerobic oxidation leads to the corresponding ketones through the acid-catalyzed decomposition of the hydroperoxides, initially formed. Thus, the aerobic oxidation of cyclooctane provides with complete selectivity cyclooctanone in the presence of catalytic amounts of NHPI and *m*-CPBA or benzaldehyde (Eq. (100)):



Conversion 40-55%, Selectivity 100%

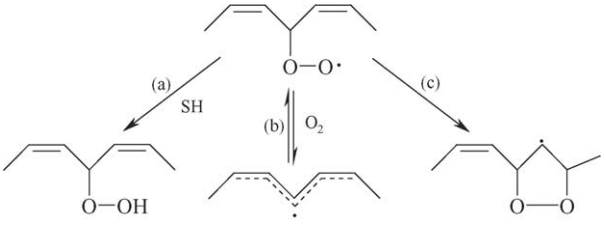
(100)



(102)

6. Aerobic peroxidation of polyunsaturated fatty acids, catalyzed by amidoxyl radicals

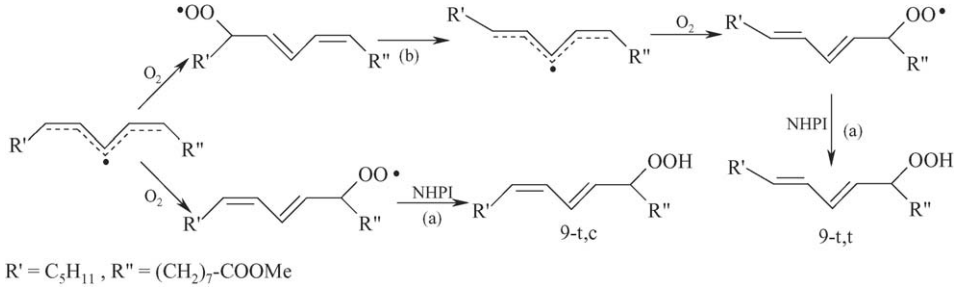
Peroxidation of polyunsaturated fatty acids and esters is of great interest in biology, due to the role that the peroxides play as modulators of enzymes [65], in biosynthetic processes [66] and above all in the origin and development of important pathologies such as tumor promotion and atheroschlerosis [67]. The availability of lipid hydroperoxides for the study and characterization of secondary oxidation products is of considerable interest. However, the direct oxidation of lipid esters by the use of free-radical initiators gives complex product mixtures, normally in yields of less than 5%, due to the competition between three main reactions of peroxyl radicals [68]: (a) hydrogen abstraction, (b) β-scission, and (c) cyclization (Eq. (101)):



(101)

Initial attempts of autoxidation of methyl linoleate, catalyzed by NHPI, provided an increase of the conversion of the methyl linoleate to hydroperoxide products [69] (four hydroperoxides, Eq. (102)):

The diastereoselectivity, however, was poor (*t*, *c*/*t*, $t = 0.8$) because the rates of β-fragmentation (b) of the peroxyl radicals competes with the hydrogen abstraction from NHPI (a) (Eq. (103)):



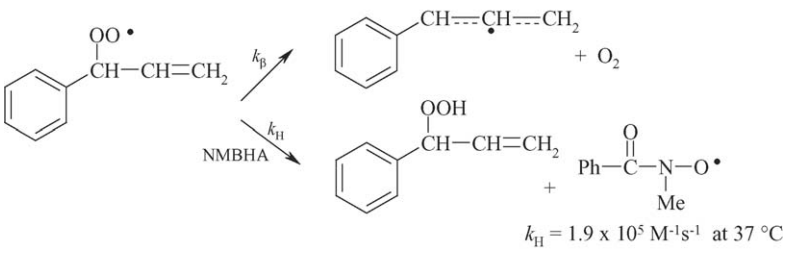
(103)

These results suggested that a better H-atom donor catalyst would be required from the selective synthesis of *trans*,*cis* hydroperoxides.

Attempts to utilize 2,2,6,6-tetramethyl-*N*-hydroxy-piperidine as catalyst were not successful because the resulting nitroxyl radical, TEMPO, being persistent, acts as inhibitor of autoxidation.

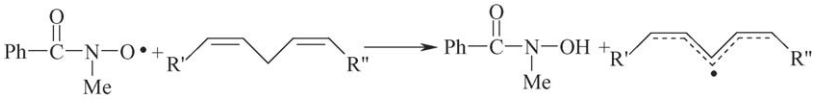
Thus, a *N*-hydroxyderivative (*N*-methyl benzohydroxamic acid, NMBHA) with a BDE value of the O–H bond (79.2 kcal/mol) intermediate between the BDEs of NHPI (88.1 kcal/mol) and *N*-hydroxy piperidine (69.6 kcal/mol) (Table 1) appeared to be a viable candidate for use as an autoxidation catalyst [69]. The hydrogen abstraction from NMBHA by the peroxyl radical was expected to be significantly faster than from NHPI ($k_{28} = 7.2 \times 10^3\ M^{-1}\ s^{-1}$ at 30 °C), based on its O–H BDE value.

A peroxyl radical clock, based on allylbenzene, was developed on the basis of the competition between a unimolecular β-fragmentation (k_β) and its bimolecular reaction with the hydrogen atom donor (NMBHA, k_H) (Eq. (102)). The clock was calibrated with α-tocopherol, which has a well-estabilished rate constant for the reaction with peroxyl radicals ($k_H = 3.5 \times 10^6\ M^{-1}\ s^{-1}$ at 37 °C) [70]. This clock has been successfully used to measure the rate constant k_H [71] for Eq. (104):

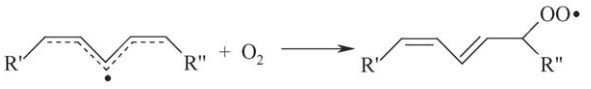


(104)

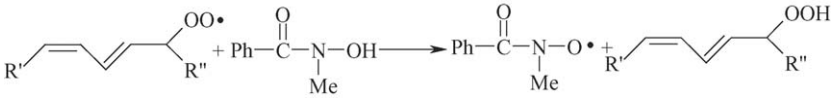
The hydrogen abstraction from bisallylic C–H bonds by the amidoxyl radical, to form a pentadienyl radical, is exothermic [72] ($\Delta H \sim -6$ kcal/mol) and that contributes to make quite effective the radical chain of oxidation catalyzed by NMBHA (Eqs. (105)–(107)):



(105)



(106)



(107)

The hydroperoxide yields of the NMBHA catalyzed oxidation of methyl linoleate and methyl linoleaidate were much higher [69] compared to the previous known methods of peroxidation. Moreover, the selectivity was particularly high: practically only the *trans*,*cis* hydroperoxides were obtained with methyl Linoleate and *trans*,*trans* hydroperoxides with linoleaidate. As good hydrogen atom donor (Eq. (107)), NMBHA minimizes the slower β-fragmentation (Eq. (101b)) or cyclization (Eq. (101c)) (10^2 to 10^3 s^{-1}) of the intermediate peroxyl radicals, conferring a higher selectivity to the system and generating an effective free-radical chain while forming the kinetically favored hydroperoxide [69].

The NMBHA catalyzed aerobic oxidation of methyl esters of polyunsaturated fatty acids with more than two double bonds was also studied. Thus, methyl α-linolenate gave four *trans*,*cis* hydroperoxides at the 16, 13, 12 and 9 positions. Similar oxidation with methyl arachidonate led to the six expected *trans*,*cis* hydroperoxides with oxygen substitution of the 15, 12, 11, 9, 8 and 5 positions of the 20 carbon chain.

The uncatalyzed aerobic oxidations gave much lower yields and much more complex mixtures of reaction products. Thus, it appears that NMBHA and, very likely, similar hydroxamic acids are particularly effective catalytic systems for the synthesis of hydroperoxides from polyunsaturated derivatives.

7. Aerobic oxidation of silanes, catalyzed by imidoxyl radicals

The BDE values of the Si–H bonds are on the average somewhat lower compared to the analogous C–H bonds suggesting the possibility of their aerobic oxidation catalyzed by imidoxyl radicals on enthalpic basis.

A main approach for silanol synthesis involves the oxidation of silanes by a variety of oxidants, such as peracids [73], $KMnO_4$ [74], $AgNO_3$ [75], $AgNO_2$ [75], Ag_2O [75], HgO [76], O_3 [77], and dioxiranes [78].

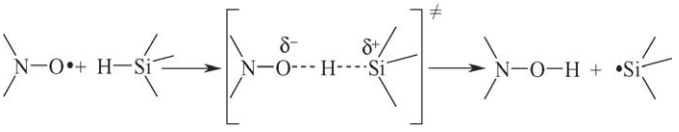
Most of these methods give the corresponding siloxanes as undesired side products or utilize expensive oxidants with environmental drawbacks.

The thermochemical data on Si–H BDE (Table 9) indicate that the factors dominating the thermo-chemistry of the C–H bonds are essentially unimportant in the silicon congeners.

The BDE values are substantially similar for different Si–H bonds in silanes, while the corresponding series of BDE values in hydrocarbons spans a range of 16 from 105 kcal/mol for methane to 88.5 kcal/mol for toluene. Thus, the hydrogen abstraction from silanes by the PINO radical are almost thermoneutral and they should also be favored by the polar effect Eq. (108) and we would expect in most cases even higher rates compared to the hydrogen abstractions from the corresponding C–H bonds:

Table 9
BDE values of Si—H and C—H bonds

	BDE (kcal/mol)
H_3Si—H	90.3
Me_3Si—H	90.3
$PhSiH_2$—H	88.2
H_3C—H	105.0
Me_3C—H	95.7
$PhCH_2$—H	88.5



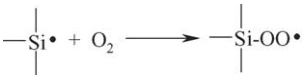
(108)

Moreover, the silanoxyl radicals do not undergo a fast β-scission as the corresponding alkoxyl radicals, as we have above discussed, so that the synthesis of silanols by aerobic oxidation of silanes, catalyzed by NHPI and Co(II) salt, appeared to be a viable selective process.

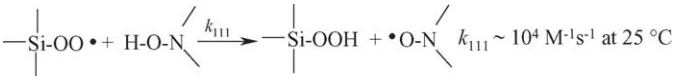
Actually we have found that silanes react with oxygen and NHPI catalysis under very mild conditions (ambient temperature and pressure) giving selectively the corresponding silanols [79] (Eq. (109)). The process is by far the most convenient among the numerous oxidations developed for this purpose:

$$2R_3SiH + O_2 \xrightarrow[Co(II)]{NHPI} 2R_3Si{-}OH \quad (>90\%) \tag{109}$$

The reaction mechanism is a redox radical chain (Eqs. (110)–(114)) similar to that of the aerobic oxidation of isopropyl-aromatics, but with the difference that silanoxyl radicals do not undergo β-scission in the presence of NHPI, so that the problem of the solvent is not crucial as in the oxidation of hydrocarbons:

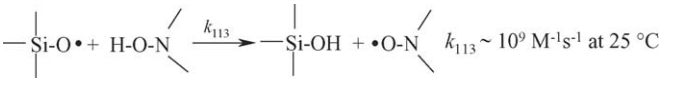


(110)



(111)

(112)

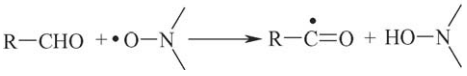


(113)

(114)

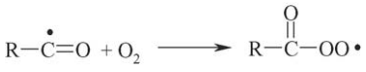
8. Acylation of heteroaromatic bases by aerobic oxidation of aldehydes

NHPI catalyzes the aerobic oxidation of aldehydes to peracids (Eq. (98)); the hydrogen abstraction by the PINO radical (Eq. (115)) plays a key role:



(115)

The acyl radical reacts fast with the oxygen giving the acylperoxyl radical, which abstracts a hydrogen atom from NHPI generating a free-radical chain (Eqs. (116) and (117)):



(116)

(117)

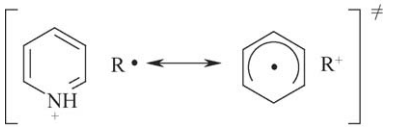
We expect that reaction (117) is faster than the hydrogen abstraction by the peroxyl radical from NHPI (7.2×10^3 M^{-1} s^{-1} at 30 °C, Eq. (28)) since it is about 5 kcal/mol more exothermic.

On the other hand the peracids formed in Eq. (117) react further on with NHPI by molecule-induced homolysis to give the PINO radical (=N–O•, Eq. (90)).

We have considered the possibility to intercept the acyl radicals generated in Eq. (115) by the so-called "Minisci reaction" [80], relative to the acylation and alkylation of protonated heteroaromatic bases by nucleophilic carbon-centered radicals.

The Friedel–Crafts alkylation and acylation have a very poor interest when applied to heterocyclic aromatic bases, while the substitution of the protonated heterocycles by nucleophilic carbon-centered radicals is quite successful.

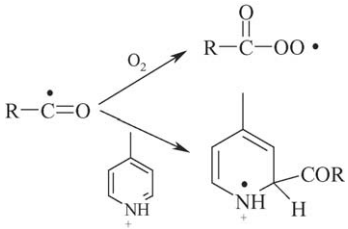
This reaction, due to the dominant polar effect which is mainly related to the charge transfer character of the transition state (Eq. (118)), reproduces most of the aspects of the Friedel–Crafts aromatic substitution, but with opposite reactivity and selectivity:



(118)

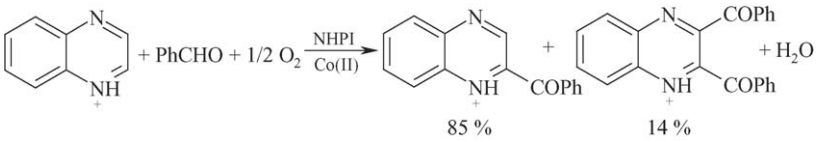
The parallelism with the Friedel–Crafts aromatic substitution arises from the fact that more stable the carbonium ion (R^+) is, the more nucleophilic the corresponding radical will generally be. Thus, in principle, all the electrophilic species used in the Friedel–Crafts reaction, when used as the corresponding radicals, behave as nucleophilic species for the selective substitution of heteroaromatic bases [81,51].

The high rate constants (from 10^5 to 10^8 M^{-1} s^{-1}) [82] for the nucleophilic radical addition to protonated heteroaromatic bases suggested to utilize the acyl radicals arising from Eq. (115) for the aromatic substitution in competition with the aerobic oxidation (Eq. (116)) by keeping low the O_2 concentration:



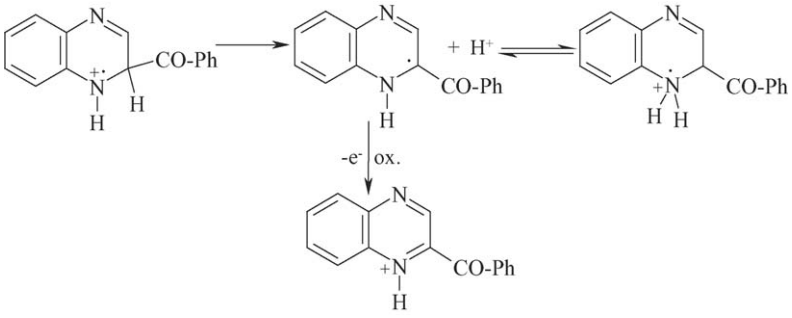
(119)

Actually the aerobic oxidation of aldehydes, catalyzed by NHPI and Co(II) salt, revealed to be effective for the acylation of protonated heteroaromatic bases [83] (i.e. Eq. (120)):



(120)

The reaction mechanism involves the addition of the acyl radical to the heterocyclic ring (Eq. (119)), followed by the oxidative rearomatization of the radical adduct (Eq. (121)):

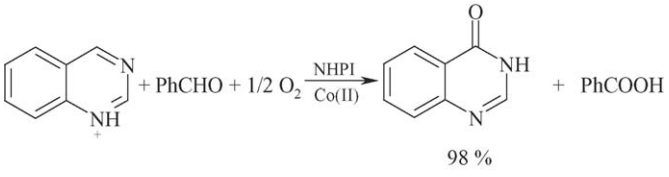


(121)

The oxidation of the radical adduct occurs by the acyl-peroxyl radical, by the peracid or by the Co(III) salt formed during the aerobic oxidation.

No acylation occurs under the same conditions in the absence of NHPI, which means that the acyl radical is generated by hydrogen abstraction from the aldehyde by PINO radicals.

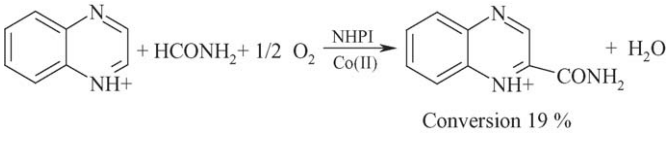
The reaction has general character for aldehydes and bases [83], with the exception of quinazoline: no acylation occurs in the last case, but 3-*H*-quinazolin-4one is the only reaction product [83] (Eq. (122)):



(122)

The result is explained by the fast oxidation of quinazoline by the peracid formed according to Eq. (117).

Attempts to free-radical carbamoylation of heteroaromatic bases by catalyzed aerobic oxidation of formamide gave much lower conversion (Eq. (123)) indicating that the reaction of the carbamoyl radical with O_2 is much faster than its addition to the heteroaromatic ring [84]:



(123)

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